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THE USE OF THE CERVICAL SPREAD IN CANCER DETECTION

An Effective Method and an Evaluation

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THE cervical spread, stained by the Papanicolaou method, is so useful that it is in danger of being looked upon as an infallible diagnostic aid—both by physicians and by patients. Some surgeons have performed hysterectomy on the sole basis of a cytologic diagnosis of cervical cancer; and patients themselves have become so imbued with the fear of cancer that the mere mention of their having an atypical or a positive "cancer spread" persuades them that immediate drastic treatment alone will avoid the consequences of the dread disease. The cervical spread has great diagnostic value only if the physician is fully aware of its specific limitations.

It is the purpose of this report to indicate some of the sources of possible error in making a cytologic diagnosis, to describe an effective cervical spread technic, and to summarize our results from its use.

Sources of Error

Cytologic study, like other laboratory studies, is subject to technical and human error. The judgment and actions of several persons are involved. They are: (1) the patient, (2) the examining physician, (3) the cytotechnician, and (4) the pathologist.

The fastidious patient usually will take a douche in preparation for a pelvic examination, not realizing that cells of diagnostic value may be washed away or destroyed. Normal findings after a douche could be false. Every woman who makes an appointment for a pelvic or a general examination should be advised to refrain from douching for from 48 to 72 hours before the examination.

The examining physician may make a digital examination first, or use an excessive amount of lubricant on the speculum; both conditions render the cervical specimen less satisfactory for cytologic examination. He may smear the material on the slide and cause clumping of the cells; he may let the slide dry before he fixes the material and thereby make a true evaluation impossible.

The cytotechnician who stains the laboratory specimens and who is responsible for the initial screening, also is subject to human error. Occasionally, even in the best-regulated laboratory, specimens will be incorrectly labeled.

The pathologist constantly must temper his interpretation with skill and judgment. In doubtful cases he may purposely record the most serious interpretation possible, in order to avoid undertreatment by the physician. The pathologist's experience and skill are hampered or enhanced according to the extent that the sources of error mentioned above are in force.

The problem of obtaining cervical specimens for spreads, and of interpreting the findings, is complex because of the chance for human error. We believe that a definite, standardized technic in obtaining specimens will provide pathologists with optimal material for evaluation, and that a simple method is less likely to be subject to human error.

An Effective Technic

Obtaining cervical spreads. The technic that we find highly effective is as follows:

1. The patient is advised to omit douches for from 48 to 72 hours prior to examination.

2. Before making a digital examination, the physician visualizes the cervix by means of a *lightly* lubricated or wet speculum.

3. He next obtains a cervical specimen. A cotton applicator stick is twirled in the cervical os and is rolled across the surface of the cervix.

4. The swab is *immediately rolled* across a clean, dry, glass slide. It must not be smeared or scrubbed on the slide.

5. The completed spread and slide are *immediately* immersed in a solution of 97 parts of 95 per cent alcohol and 3 parts of glacial acetic acid. The slide is taken to the laboratory in this solution.

6. The spread is stained by the Papanicolaou method.[1]

Classifying results, and further study. Results in our practice are designated as negative or positive for atypical cells. Results positive for atypical cells are grouped according to compatibility with (1) malignancy (invasive carcinoma), (2) carcinoma in situ, (3) carcinoma in situ or severe dysplasia, (4) severe dysplasia. The first two groups correspond to Papanicolaou's[1] class V, and the remainder to his class IV.

Positive-cell findings demand further study. If a questionable lesion is seen, a biopsy specimen is immediately obtained. If no gross cervical lesion is visible, a sharp-knife conization is performed. This procedure will provide the pathologist with a ring of tissue, including the squamocolumnar junction that has not been distorted by heat as in a cautery conization. The specimen is cut into serial blocks and usually about 12 sections are examined.

Sharp-knife conizations may be performed with a standard number 11 or 12 Bard Parker knife blade employing a sawing motion. After the conization the cervix will require hemostasis and often it is somewhat irregular. A Bovie cautery conization and electrocoagulation are immediately performed.

Review of Results

A total of 22,716 cytologic specimens of cervical origin were studied in the pathology laboratory of the Cleveland Clinic between October 1, 1951, and May 31, 1957. So far, 104 cases of invasive squamous-cell carcinoma and 110 cases of carcinoma in situ have been found. In an earlier study[2] the spread technic was accurate in 94 per cent of the diagnoses later histologically confirmed as preinvasive or invasive cervical carcinoma. Fifteen per cent of the cases of invasive carcinoma were detected from the cervical spread in the absence of a visible lesion. Four per cent of the spreads were false-positive—cytologically positive and unsubstantiated histologically. This percentage was obtained by dividing the total number of histologically unsubstantiated—cytologically positive spreads by the total number of cytologically positive spreads. Thus, when a positive spread is reported, the chance of a later negative histologic report on biopsy is 1 in 25.

Comment

The cervical spread technic is designed to help detect lesions that deserve more meticulous study than is afforded by the unaided eye. There is no doubt that where facilities are adequate, the cytologic study should be employed. Cervical spread does not supplant biopsy—it supplements biopsy. All women between 30 and 60 years of age who have no gynecologic symptoms should have

a cervical spread made at least every 18 months. The technic may be employed more frequently if bleeding irregularities occur. After a spread has been made, a suspicious lesion should be biopsied and studied histologically. Where laboratory facilities are limited and personnel are inexperienced in cytologic interpretation, frequent meticulous inspections of the cervix, and biopsies of all erosions or cervical abnormalities, are preferable to poorly executed spreads and unskillful cytologic interpretation.

Summary

The cervical spread technic for cytologic diagnosis could fall into disrepute unless certain precautions are constantly employed in obtaining the specimens and in interpreting the results. The possible sources of error or failure are primarily related to human factors and those persons concerned are the patient, the examining physician, the cytotechnician, and the pathologist.

The simpler the method for obtaining material and making the cytologic study, the less likely it is to be subject to error. Such a method is described.

Although the results obtained from cervical spreads have a high degree of accuracy, histologic confirmation must be obtained before an exact diagnosis can be made and treatment instituted.

References

1. Papanicolaou, G. N.: New procedure for staining vaginal smears. Science **95:** 438-439, April 24, 1942.

2. McCormack, L. J.; Belovich, Doris, and Krieger, J. S.: Invasive carcinoma of cervix uteri; cytohistologic study. Am. J. Clin. Path.: In press.

THE HYPERTENSION-REDUCING FUNCTION OF THE KIDNEY

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THE recent synthesis of angiotonin (hypertensin) II by members of this Division[1] has opened important vistas in the search for participation of humoral agents in the genesis of hypertension.

Angiotonin when injected into an experimental animal or a human being causes a rise in blood pressure. Does it follow that its pressor activity is responsible for human hypertensive cardiovascular disease or even for chronic experimental renal hypertension? Enough data to answer this question are not yet available.

In our enthusiastic recognition of the pressor substances, we should not forget that although the participation of the renin-angiotonin system in experimental renal hypertension seems beyond doubt, many phenomena can be better explained if it is assumed that the kidney in addition to its excretory function has two opposing blood-pressure-regulating functions. One of these is the liberation of renin. Renin acts on renin-substrate to form angiotonin. The second is the formation of a material that reduces elevated blood pressure.

I shall present a working hypothesis developed by Dr. Irvine H. Page and myself for the pathogenesis of hypertensive cardiovascular disease, which takes into account the experimental evidence obtained in animals deprived of their kidneys. The hypertension that then occurs is called "renoprival" hypertension. This review is not complete. I shall mention the facts that support our views and leave it to others to contradict them. I shall quote mainly from our own published work. Due credit to earlier investigators has been given in those earlier publications; here the concern is not with priority of accomplishments but with the possible relationship of the facts.

Section I

Dogs from which both kidneys have been removed develop hypertensive cardiovascular disease.[2] Figure 1 shows that the regimen on which the dogs are kept after bilateral nephrectomy has some influence upon the rate at which hypertension develops. Overhydration with electrolyte solution increases the rate during the first few days,[3] but avoidance of severe overhydration as judged by constancy of body weight does not prevent the development of renoprival hypertension. A high-protein diet[4] seems to encourage the development of hypertension, especially in rats[5]; frequent peritoneal lavage does not prevent or

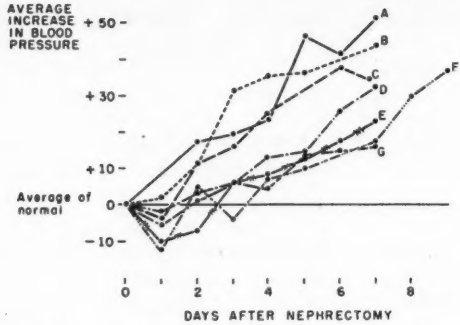

Fig. 1. Renoprival hypertension. Average increase above the normal arterial pressures in 7 groups of nephrectomized dogs.

Group	No. of dogs	Nephrectomy, no. of stages	Overhydration	Dialysis	Diet: 4-6 gm. protein/kg./day	Diet: 16 ml. saline/kg./day
A	7	One	++	—	—	—
B	6	Two	++	—	—	—
C	3	One	++	++	—	—
D	3	One	—	+	—	—
E	2	One	—	+	+ (kidney)	—
F	5	One	—	+	+	+
G	5	One	—	+	— (vomiting or unfed)	—
Total	31					

Reproduced through the courtesy of the American Journal of Physiology.[4]

modify it.[4] Variations in the amount of serum sodium in the nephrectomized dog can influence the height of blood pressure.[6] This relationship is seen in Figure 2, where the experimental variations in serum sodium were followed by changes in blood pressure; this is not a phenomenon limited to renoprival hypertension since other forms of hypertension also are susceptible to changes in serum sodium.

Extrarenal factors have been blamed for renoprival hypertension. The adrenals well may be excluded as a decisive factor since Turner and Grollman[7] produced renoprival hypertension and vascular disease in dogs from which both kidneys and adrenals had been removed.

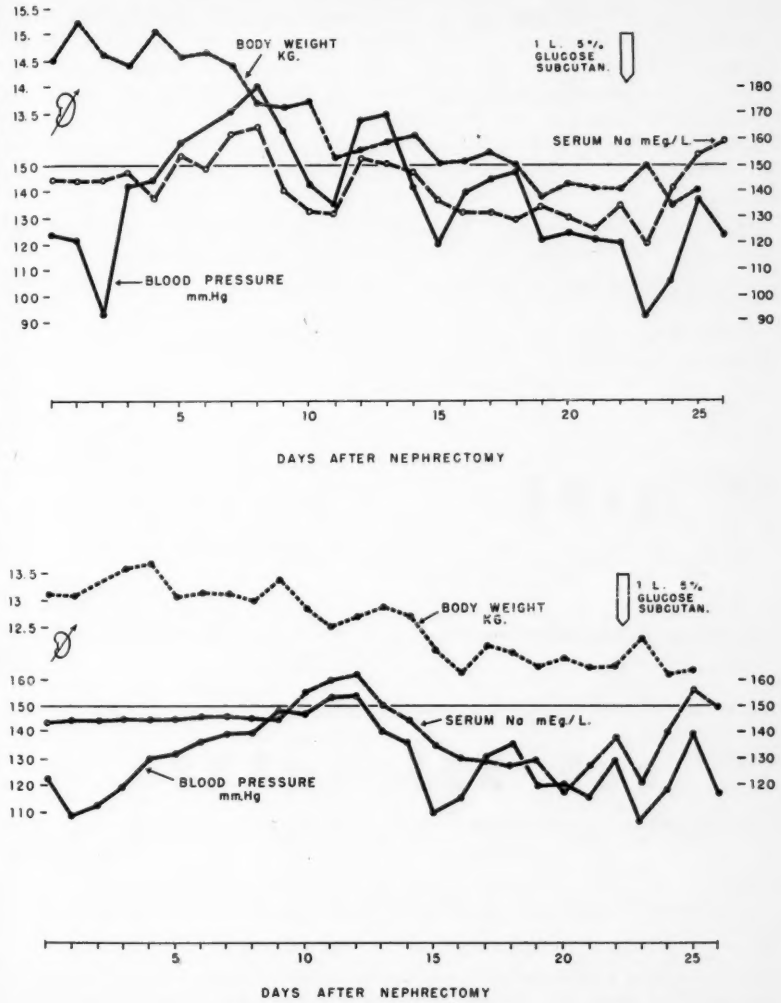

Fig. 2. Courses of two dogs in which serum sodium was deliberately varied. Both graphs show an association between the changes in serum sodium and arterial pressure independent of body weight. Sodium content of dialyzing fluid was varied in the experiment above from the fifth day on, and in that below from the eighth day. Initial rinsing fluid sodium was 148 mEq./l. and the subsequent concentrations 168 and 128 mEq./l. Hypodermoclysis with 5% glucose on the 22nd postnephrectomy day, in both experiments, caused gains in weight and decreases in serum sodium concentration and arterial pressure. *Reproduced through the courtesy of the American Journal of Physiology.*[6]

Some experimental animals do not develop renoprival hypertension after nephrectomy. This may be due to several factors: (1) an "untreated" non-dialyzed nephrectomized dog is not a happy animal and is not a qualified "control." It is likely to be sick with vomiting, uremia, dehydration, or shock. (2) The observation time may be too short. (3) Occasionally, the dog does not follow the pattern.[4] There is no obvious reason. Figure 3 shows the graphs of the courses of two dogs: one developed renoprival hypertension, the other did not.

As we have seen, renoprival hypertension occurs rapidly in nephrectomized dogs that are overhydrated by intraperitoneal injection of electrolyte solution. However, hypertension does not occur in similarly overhydrated dogs with

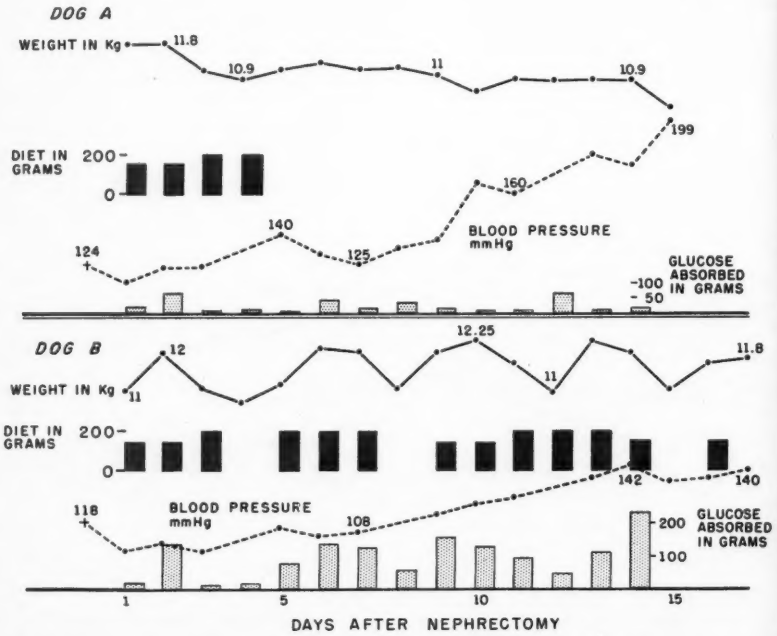

Fig. 3. Courses of arterial pressure in two nephrectomized dogs maintained for 15 or 17 days with peritoneal lavage. *Dog A* (upper half of the figure) developed hypertension notwithstanding loss in weight, discontinuance of forced feedings on the 4th day, and failure to absorb appreciable amounts of glucose from the peritoneal lavage fluid. *Dog B* (lower half of the figure) had only a small increase in arterial pressure, notwithstanding maintenance of weight, adequate dietary intake and absorption of sufficient glucose from the peritoneal lavage fluid. The average serum sodium and potassium and the blood urea levels were closely comparable in both dogs. *Dog A*—Serum Na, 148 mEq./l. (147-150); serum K, 4 mEq./l. (3.5-4.7); blood urea on the 12th day, 144 mg.%. *Dog B*—Serum Na, 148 mEq./l. (147-150); serum K, 4 mEq./l. (3-4.6); blood urea on the 12th day, 144 mg.%. *Reproduced through the courtesy of the American Journal of Physiology.*[4]

kidneys, but whose ureters are transplanted into the venae cavae. This is beautifully shown in an experiment first reported by Grollman, Muirhead, and Vanatta,[2] and later by us,[6] which contrasts the effects of nephrectomy with those of ureteral transplantation (Fig. 4). These experiments show that even if the excretory function of the kidney is frustrated by having the urine led back into the blood stream, the mere presence in the body of functional renal tissue

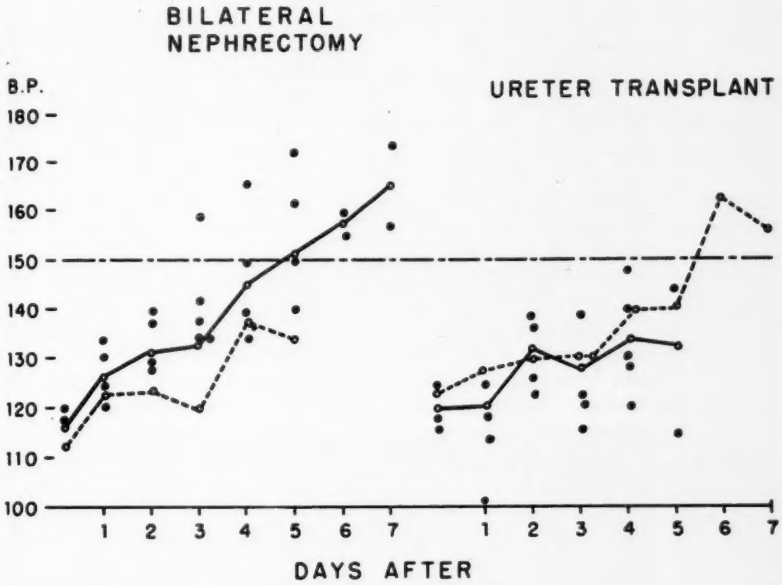

Fig. 4. Comparison of dogs after bilateral nephrectomy and dogs after ureteral transplantation into the vena cava.

Group	Prep.	No. of Dogs	Time of Obs., days	Wt. Increase, %	Serum Na, mEq./l.	Av. Highest B.P., mm. Hg	No. of Dogs With		
							Hypertension	Arteriolar necrosis	'Grotesque' edema of gastric mucosa
1	One-stage bilateral nephrectomy	7	4-7	29 (18-44)	150 (138*-160)	160 (140-172)	6†	4	6
2	Ureteral transplantation into vena cava	7	4-7	29 (12-49)	150 (135*-157)	139 (125-165)	1†	2‡	0

All dogs greatly overhydrated by filling the peritoneal cavity with electrolyte solution. *Lowest value found corrected same day with NaCl. †The one exception that developed no hypertension suffered from a necrotic intussusception. ‡The one exception that developed hypertension had pyelonephritis and hydronephrosis; it also had arteriolar necrosis. *The table is reproduced through the courtesy of the American Journal of Physiology.*[6]

protects against the development of hypertension. This then is a demonstration of a protective nonexcretory function of the kidney, a function that prevents an abnormal rise in blood pressure.

In conclusion: *Although a variety of factors influences the occurrence or the rate of development of renoprival hypertension, the essential factor in its pathogenesis is "the absence of renal tissue."*

Section II

Those who disagree with the concept of renoprival cardiovascular hypertension sometimes argue that renoprival hypertension actually is not high enough to be true *hypertension*. It is admitted that in trained*, unanesthetized, renoprival hypertensive dogs, the mean arterial pressures taken by direct puncture of the femoral artery often are not higher than 160 mm. Hg. They are significant only in contrast to those in prenephrectomy controls, but elevations to more than 200 mm. Hg do occur. It seems to me that more important than the actual elevation of the blood pressure are the vascular changes that take place.[8] Figures 5 through 10 show necrotizing and fibrinoid changes in the media of arterioles and proliferative changes under the intima of small vessels in dogs, and necrotic changes in the aorta of a rat. All these animals had renoprival cardiovascular disease. Some investigators have proposed and others have denied that many of the pathologic changes here depicted are identical or similar to vascular changes seen in human cardiovascular disease.

In conclusion: *Our experiments support the view first vigorously expressed by Grollman[2] that there is a kind of hypertensive cardiovascular disease that depends on the absence of renal tissue for its existence,* and I believe that the same pathogenesis occurs in human hypertensive cardiovascular disease.

Section III

Is it possible that renoprival hypertension is caused by renin or its reaction product, angiotonin? In Belgium and in Spain it was formerly believed that renin of extrarenal origin might be a factor in hypertensive disease. With the help of Dr. George E. Wakerlin in Chicago and Dr. Erwin Haas in the laboratory of Dr. Harry Goldblatt in Cleveland, we have tested this hypothesis.[9] Dogs were protected with antirenin either by injection of antirenin serum or by active immunization with renin. Determinations of antirenin activity in the blood serum demonstrated a concentration of at least 10 units per milliliter in each dog. These animals showed virtual absence of a rise in blood pressure after the injection of renin. For these reasons it is assumed that they were well protected against renin.

**A trained dog here means a dog that does not actively resist lying on the table and has become used to puncture of the femoral artery.*

Fig. 5. Fibrinoid necrosis of intestinal arteriole of dog. Masson stain, X 150.

Fig. 6. Fibrinoid degeneration of arteriole of intestine of rat. X 300.

Reproduced through the courtesy of Laboratory Investigation.[8]

Fig. 7. Vessel of dog showing focal fibrinoid change and partial occlusion of lumen. X 150.

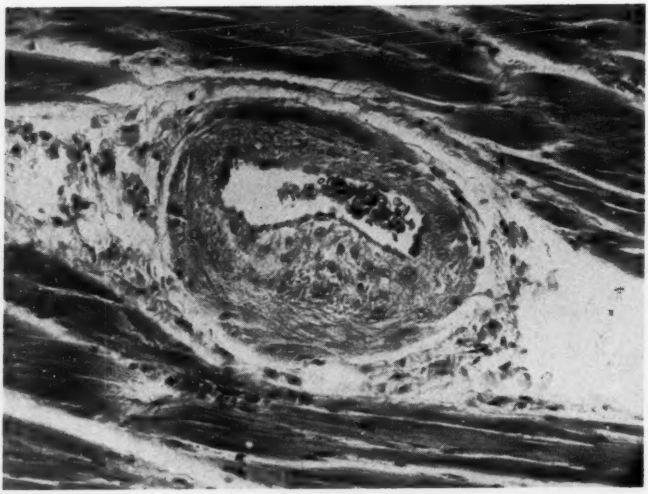

Fig. 8. Myocardial arteriole of dog, demonstrating proliferative change. X 300.

Reproduced through the courtesy of Laboratory Investigation.[8]

Fig. 9. Proliferative vascular lesion in dog. X 300.

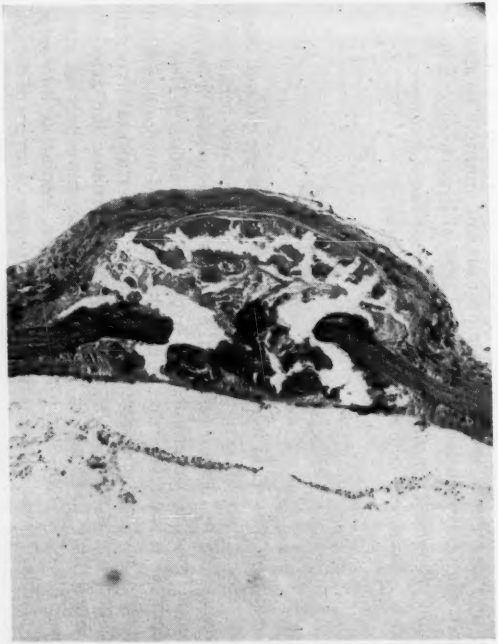

Fig. 10. Extreme necrosis and cystic change in aortic media of rat. X 70.

Reproduced through the courtesy of Laboratory Investigation.[8]

The suppression of renin by antirenin did not prevent the development of renoprival hypertension in overhydrated nephrectomized dogs (Fig. 11) or reduce it in normally hydrated renoprival hypertensive dogs (Fig. 12). Nor did it prevent the development of the arteriolar necrosis and multiple focal myocardial hemorrhagic necrosis associated with renoprival hypertensive disease.[9]

In conclusion: *Renoprival hypertension and its associated vascular changes are not attributable either to residual renin or to renin of extrarenal origin.*

Section IV

If chronic experimental renal hypertension* were due to the pressor effect of continuously released angiotonin, the hypertension should not persist after total nephrectomy. Figure 13 shows that if the kidneys are removed from dogs with experimental renal hypertension, the hypertension persists.[10] How can this be explained? (a) It is unlikely that circulating renin and angiotonin would persist so long; (b) it has been suggested that in chronic experimental hypertension the blood pressure is maintained at its high level because the arterioles have become irreversibly hardened or the carotid sinuses have become reset. However, Floyer[11,12] has shown that these mechanisms, insofar as they exist, are quickly reversible. Floyer removed the clip from the renal artery of the sole remaining kidney in rats with renal hypertension. Promptly after the removal of the clip the blood pressure went down to normal. Thus, if the results obtained in rats can be trusted, it can be concluded that the arteries are not hardened and the sinuses evidently can be easily reset. It will be shown later that the same prompt fall in blood pressure occurs after transplantation of normal kidneys in a hypertensive dog, and that a comparable fall occurs after such a procedure in man.

We have seen that renoprival hypertension takes a few days to develop. However, if the kidneys are removed from dogs having chronic experimental hypertension, the blood pressure does not first fall and then gradually rise again, but rather remains unchanged.[10,11] An explanation might be that the same mechanism underlies both renoprival and renal hypertension. The working hypothesis is now as follows: *Chronic experimental renal hypertension and hypertensive cardiovascular disease are not caused by the direct pressor action of the renin-angiotonin mechanism, but depend on the same mechanism that causes renoprival cardiovascular disease.*

Section V

It is known that renal hypertension develops in some animals, especially in rats, when a clamp is applied to the renal artery of only one kidney.[11] Evidently the normal kidney is not able to counteract effectively the

*Acute or acute malignant hypertension, which well may be caused by direct pressor effect of angiotonin, is not under consideration here.

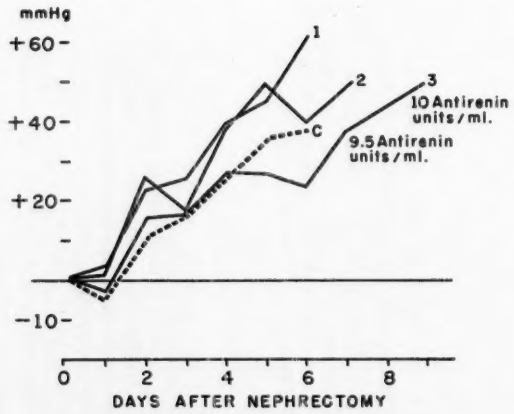

Fig. 11. Rise in blood pressure above the average before operation in 3 nephrectomized overhydrated dogs after prophylaxis with antirenin, as compared to average rise in blood pressure of 3 dogs without antirenin. *C*—average change in blood pressure in 3 controls; *dog 1*—antirenin serum injected on the day of and following nephrectomy; *dog 2*—antirenin serum injected on the day of and following nephrectomy; *dog 3*—treated with renin injections until antirenin titer 9-10 U/ml., thereafter nephrectomized.

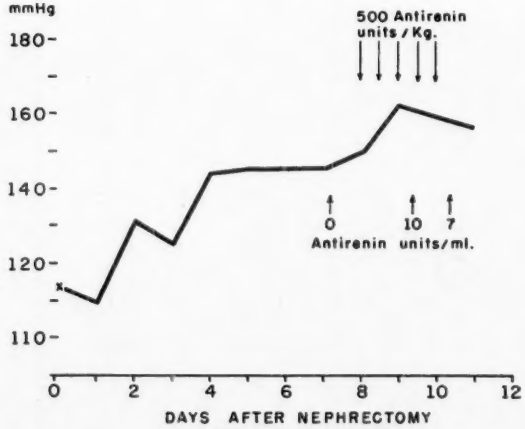

Fig. 12. Effect of antirenin on renoprival hypertension in a dog without overhydration, *dog 4. Large arrows* indicate the injections of antirenin serum (Wakerlin). The antirenin titer of the blood serum is indicated under the *small arrows* and was found to rise from 0 to 10 antirenin units/ml. In *dog 5* (not shown) the antirenin titer rose from 0 to 15 AU/ml.; the course of the blood pressure was almost the same.

Reproduced through the courtesy of the American Journal of Physiology.[9]

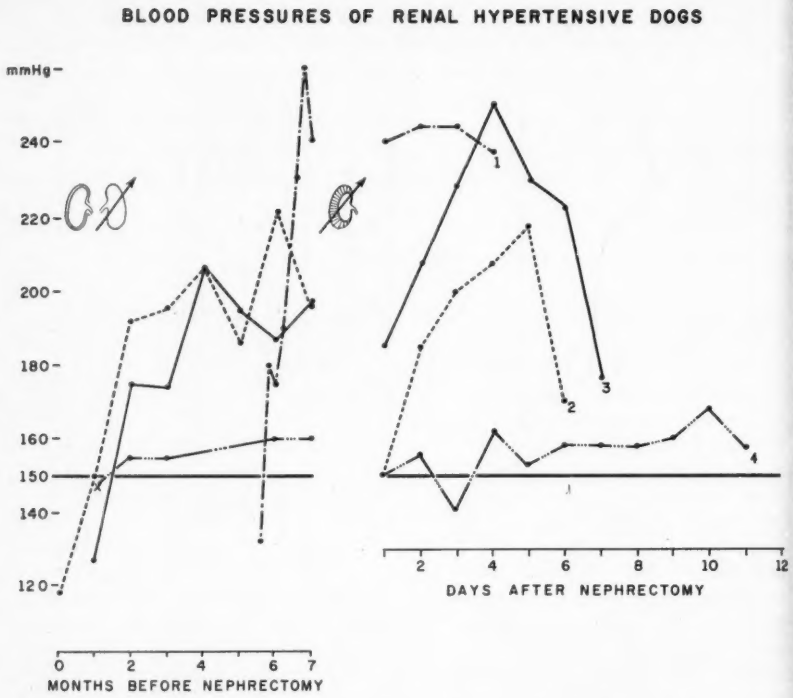

Fig. 13. Arterial blood pressures in dogs with renal hypertension before and after nephrectomy. *1.* Malignant hypertension of five weeks' duration; persisted after nephrectomy. *2.* Renal hypertension of 7 months' duration; persisted after nephrectomy (after reduction to 150 mm. Hg on 1st day only). *3.* Renal hypertension of 4 months' duration; persisted with temporary increase after nephrectomy. *4.* Only mild hypertension (160 mm. Hg) after the kidney slipped out of a rubber capsule; after removal of that kidney, blood pressure stayed around the same level. *Reproduced through the courtesy of the American Journal of Physiology.*[10]

hypertensive action of the clamped kidney. The originally normal, let us with Floyer[11] call it the "untouched" kidney, after some time participates in the maintenance of the high blood pressure. After the removal of the clamp from the clamped kidney,[11] but leaving the untouched kidney in place, the blood pressure comes down but not to a normal level. Removal of the previously clamped kidney, leaving the untouched kidney in the body, will result in a mild hypertension. However, removing the untouched kidney, leaving only the clamped kidney from which the clamp has been removed, reduces the blood pressure to a normal level. A possible explanation of this phenomenon is that *a*

clamped or otherwise damaged kidney produces something (possibly renin) which impairs, blunts, or destroys that function of the other kidney that is normally concerned with reduction of hypertension. The amount of renin to effect this blunting might be very much smaller than the amount necessary to produce an immediate pressor response.

This hypothesis provides an explanation for the well-established blood-pressure-reducing effect of antirenin.[13] Antirenin would block this very small amount of renin, remove the blunting effect of renin, and re-establish the blood-pressure-reducing function of the kidneys. That antirenin is unable to exert a beneficial effect in renoprival hypertension has already been established, and Shipley[14] has shown that antirenin will not reduce the blood pressure in a renal hypertensive dog after total nephrectomy. Shipley performed only one experiment; if his findings can be confirmed they will indicate that *antirenin for its beneficial effect needs the presence of the good function of the kidney.*

Section VI

If it is true that hypertensive cardiovascular disease is caused by the absence of a specific renal function, then it should be possible to reduce hypertension by transplantation of normal kidneys. Muirhead and associates[15] showed that in dogs having renoprival hypertension, blood pressure became normal after transplantation of normal kidneys. We produced hypertension in dogs by bilateral nephrectomy and overhydration with electrolyte solution. We then transplanted a pair of normal kidneys to the neck of each dog by means of a special technic that avoids even temporary ischemia during the transfer of the kidneys (Fig. 14). Within two hours after a pair of normal kidneys were included in the circulation[16] the arterial pressure was reduced in 9 of 10 hypertensive

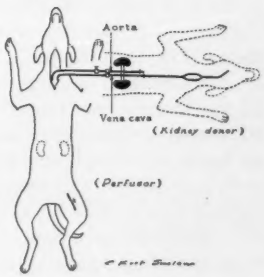

Fig. 14. Kidney perfusion according to Brull.[23,24] Blood flowed from the carotid artery of the perfusor to the lower part of the aorta and kidneys from another dog and returned via the vena cava and finally to the jugular vein of the perfusor. The dog furnishing the extra kidneys was removed when the circulation with the perfusor had become established. A pipette was used to measure flow in the vena cava. *Reproduced through the courtesy of the American Journal of Physiology.*[16]

dogs (Fig. 15). The blood-pressure-reducing ability of the kidneys in renoprival hypertension does not depend on excretion of water or changes in electrolyte balance. *These experiments support the theory that renoprival hypertension is due to the absence of a specific nonexcretory renal function.*

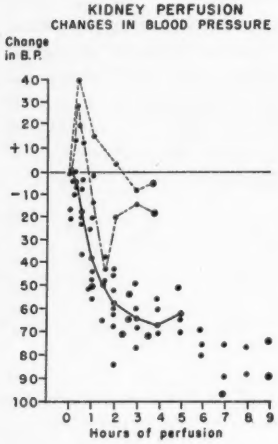

Fig. 15. Changes in blood pressure in mm. Hg of 10 nephrectomized, overhydrated and hypertensive dogs during perfusion of kidneys (*small dots*). The blood pressure came down 42-82 mm. during the first 2 hours of the perfusion in 9 of the 10 dogs. It tended to stabilize thereafter and in two dogs perfused for 9 hours it stayed around −75 and −88 mm. *Solid line* indicates the average fall in blood pressure in 8 dogs. *Heavy dots* indicate blood pressure values at end of kidney perfusion.

In one dog, indicated by a dotted line, after an initial fall of 43 mm. there was a secondary rise.

One exception in the 10 dogs with no fall in pressure occurred, also indicated by a dotted line. It showed a pressor response at the onset of perfusion. *Reproduced through the courtesy of the American Journal of Physiology.*[16]

Section VII

I have performed renal transplantations in other renoprival hypertensive dogs and confirmed the above-mentioned results. I have tried to obtain the same results in dogs with experimental renal hypertension produced by wrapping the kidneys with Cellophane.[17,18] Transplantation of a pair of normal kidneys to the neck of each of 15 dogs with such experimental renal hypertension reduced the arterial pressure significantly in 6 dogs within a period of two hours of perfusion (Fig. 16). The reduction of blood pressure is not a mechanical effect since similar perfusion of a pair of hind legs did not lower the blood pressure, nor did a large arteriovenous anastomosis produce a lowering of the pressure. Although the results of these experiments were less conclusive than those obtained from the perfusion of transplanted kidneys by renoprival hypertensive dogs, they may be indicative of the antipressor action of the transplanted kidney. In the present experiments it may have been counteracted by renin-angiotonin produced by the Cellophane-wrapped kidneys. The blood pressure reduction was more easily obtained after transplantation of large kidneys than of small kidneys. In four additional experiments in which there was at least 8 gm. of transplanted kidney

available for each kilogram of body weight of the perfusor, adequate reduction in blood pressure occurred in all four during the perfusion. These experiments are difficult to perform and any factor, such as blood loss, which is damaging to the perfusor dogs, will tend to produce a fall in blood pressure and may be erroneously interpreted as a positive result. *These experiments suggest that experimental renal hypertension may be reduced by the blood-pressure-reducing function of transplanted kidneys.*

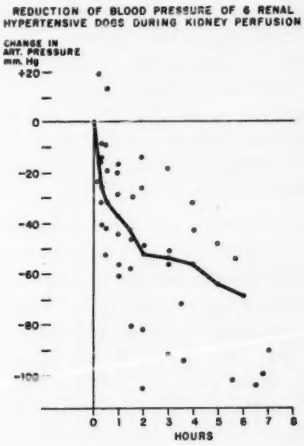

Fig. 16. In 15 dogs with experimental renal hypertension, pairs of kidneys were transplanted to the necks. In 6 of the 15 a significant fall in blood pressure occurred during the first two hours after onset of perfusion. The line indicates the average fall in blood pressure in these 6 dogs.

In 5 of the 15 dogs a fall in blood pressure occurred within 2 hours which was not considered to be significant.

In the 4 remaining dogs, no fall in blood pressure occurred after transplantation of a pair of kidneys to the neck. *Reproduced through the courtesy of the University of Michigan Regional Conference Symposium on Basic Mechanisms of Arterial Hypertension.*[18]

Section VIII

Fortunately there is support for this theory from experience with patients treated by Merrill, Murray, Harrison, and Guild.[19] The course in one of their patients is summarized below.

A 24-year-old man had chronic renal failure, probably on the basis of

bilateral pyelonephritis, with severe uremia and hypertension progressing to malignant hypertension with a blood pressure of 220/146 mm. Hg. The optic fundi showed papilledema of two diopters with white patches and hemorrhages. A normal left kidney was removed from his identical-twin brother and was transplanted to the right iliac fossa of the patient. The postoperative course was smooth. The blood-urea concentration dropped to normal and the resting blood pressure to 120/60 mm. Hg. The optic discs returned to normal. The retinal vessels became normal although a few old scars persisted in the optic fundi. Three months after homotransplantation of the kidney, the arterial pressure gradually rose to 152/90 mm. Hg. A left nephrectomy was performed. Five and one-half months after the homotransplantation, his right kidney also was removed because of persistent mild pyuria and mild labile hypertension. After this, the blood pressure really dropped to normal, and 11 months after the homotransplantation of the normal kidney the blood pressure ranged from 125/70 to 146/82 mm. Hg. The patient was active without restriction and had no apparent physical disability.

After transplantation of a normal kidney the blood pressure of this patient with malignant hypertension was lowered. This may be interpreted as evidence of the blood-pressure-reducing function of the transplanted kidney. The pressure started to rise again until the patient's own contracted kidneys were removed. The contracted kidneys apparently impaired or blunted the blood-pressure-reducing function of the normal transplanted kidney. Dr. Warren R. Guild, the Acting Director of the Cardiorenal Laboratory during Doctor Merrill's absence, wrote me that two other twins have successfully received transplanted kidneys. The course of blood pressure in these two patients has been similar to that of the first twin to receive a transplanted kidney.

The number of hypertensive patients to receive a kidney transplanted from an identical-twin brother or sister undoubtedly will increase. The clinical experience thus obtained will obviate the need for more transplantation of dog kidneys such as we have described. *Men and dogs with hypertensive cardiovascular disease so far have shown the same favorable response to renal transplantation. This implies that the mechanism of the disease is the same in both.*

Section IX

The blood-pressure-reducing function of the kidney is not an excretory one. It is not known whether it depends on production of a substance that controls high blood pressure, or on the removal of something pressor from the blood. It is to be hoped that the kidneys produce an incretory, antipressor substance, a hormone that is released into the blood stream, since such a substance may be isolated and used in treatment. Page and co-workers[20] prepared renal extracts that had blood-pressure-reducing activity. As these were protein-rich it was difficult to dissociate the nonspecific foreign-protein reactions from the

specific hypotensive effects. Grollman has concentrated his efforts on a different renal antipressor substance[21] which has smaller molecules, is dialyzable, and is active when given by mouth. He[22] believes that it may be the same as a substance found in certain marine oils. It is difficult to evaluate hypertension-reducing substances since they should not lower a normal blood pressure. However, it is possible to produce chronic hypertension in rats and dogs, and these animals are in current use in screening tests.

No investigator should be satisfied until the hypothetical hypertension-reducing substance is purified or synthesized and made available to those who need it.

Summary

Renoprival and chronic renal hypertension may both depend on the same mechanism since hypertension persists after total nephrectomy.

Renoprival hypertension possibly is caused by the absence of a nonexcretory renal function.

Renoprival hypertension can be cured by kidney transplantation. In dogs the reduction of blood pressure occurs within two hours if the transplanted kidneys have not been subjected to ischemia during the transfer.

Chronic renal hypertension may be caused by the blunting or destruction of the blood-pressure-reducing renal function by amounts of angiotonin too small to cause a direct pressor effect.

Chronic experimental hypertension can be cured by the administration of antirenin, which may free the kidneys from the blunting effects of angiotonin. Antirenin is effective only when there is good renal tissue in the body.

Chronic renal hypertension both in experimental animals and in man may be reduced or abolished by: (1) Removal of the source of production of renin. This is effective only when sufficient unimpaired renal tissue is available to exert its blood-pressure-reducing effects. (2) Transplantation of a normal kidney. In man it seems that the diseased kidneys must be removed to maintain the beneficial, blood-pressure-reducing effect.

It seems likely that the blood-pressure-reducing function of the kidney depends on a substance increted into the blood stream. Serious effort should be made to isolate such a substance.

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BRONCHIAL ADENOMA

A Clinicopathologic Study of 21 Cases

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BRONCHIAL adenoma diagnosed clinically and bronchoscopically was reported by Kramer[1] in 1930; two years later Wessler and Rabin[2] designated bronchial adenoma as a definite clinicopathologic entity. The same type of tumor had been described by Ephraim[3] in 1911 as "sarcoma of alveolar pattern," by Kreglinger[4] in 1913 as "cylindrical cell sarcoma," and by Geipel[5] in 1931 as "benign basal cell cancer."

In 1937 Hamperl[6] published a meticulous histologic study of the disorder and suggested that the adenoma was derived from mucous glands of the bronchi. He described nine cases; in two the histologic pattern was similar to the cylindromatous pattern of certain salivary gland tumors so he referred to the neoplasms as "cylindromas." Five of the remaining seven cases Hamperl called "carcinoid variant" on the basis of the resemblance of the histologic pattern to that of carcinoid tumors of the appendix reported previously. In the remaining two neoplasms, he found a special type of epithelial cell that he called an "oncocyte," a cell that he believed was present in other parts of the body besides the salivary glands, such as thyroid, parathyroid, pancreas, liver, and pituitary gland; he was unable to determine whether oncocytes have a function.

Concerning the possible etiology of bronchial adenoma, Stout[7] in 1943 reported finding all of the features of the oncocytes previously described by Hamperl.[6] Stout stressed the great difference between the oncocytes and other cells in the bronchial mucous membrane, and concluded that the oncocyte warrants serious consideration as the probable cell of origin, for no other cell, either in the bronchus or in the surrounding lung, offers itself as a possible origin of the bronchial neoplasms. To him, the presence of oncocytes in the bronchial glands and their ducts, and the absence of oncocytes from the ciliated lining cells of the mucosa offered further support to this concept.

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This etiologic concept has not satisfied all observers. Womack and Graham[8,9] found bone and cartilage in the tumors and expressed the belief that bronchial adenomas originate from arrested bronchial buds rather than from the mucous glands of the bronchi and their ducts. They noted that sometimes associated with these "mixed tumors," as they preferred to call them, were various congenital anomalies. The most frequent associated congenital anomaly was abnormal lobulation of the affected lung, and the next most frequent was the abnormal course of accessory bronchi direct from the trachea to the affected lung. These observations supported their belief that bronchial adenomas originate from anlagen that have failed to develop normally.

The theory of Womack and Graham was criticized first by Mallory[10] on the basis that bone may form in any pulmonary tumor as a result of stromal metaplasia, and that the fragments of cartilage found in some bronchial adenomas may be regarded as remnants of bronchial cartilage surrounded by infiltrating tumor strands. Furthermore, in none of the 20 specimens of bronchial adenomas studied by Stout[7] was bone or cartilage an integral part of the tumor; for this reason he agreed with Mallory[10] that the hypothesis of Womack and Graham[8,9] concerning the etiology of these tumors has insufficient foundation. Most recent observers adhere to this criticism of Womack and Graham's theory and accept the viewpoint of Hamperl and Stout that bronchial adenomas originate from the bronchial glands and their ducts.

Bronchial adenomas have been the source of considerable controversy as to the degree of their aggressive potentialities. The first published case of metastasis from the lesion was that of Zamora and Schuster[11] in 1937. In 1941, Goldman and Stephens[12] reported 18 cases of bronchial adenoma without a single case of vascular invasion or distant metastasis. They classified these neoplasms as epithelial in origin with growth potentialities midway between distantly metastasizing carcinomatous lesions and entirely local polypoid bronchial tumors. In 1942, Adams, Steiner, and Block[13] reported five cases, three of which metastasized respectively to lumbar vertebrae, to liver, and to a tracheal bronchial lymph node. In 1943, Anderson[14] reported a case that he labeled "malignant adenoma" because of hepatic metastasis. Stout[7] called these neoplasms "adenomatous," but objected to the descriptive term "benign" because of the aggressive infiltrative growth displayed by many of them and the occasional occurrence of metastasis.

Moersch and McDonald[15] expressed the belief that a bronchial adenoma should be considered as a carcinoma of low-grade malignancy, which possesses the ability to metastasize, and that when metastasis occurs to the liver, the patient's condition rapidly deteriorates as a result of hepatic insufficiency.

More recently Liebow[16] stated that bronchial adenomas could be easily differentiated from bronchogenic carcinoma because of the following characteristics of the adenomas: slow rate of growth and late recurrence, only slight tendency to destroy despite some tendency to invade adjacent tissue, and rare, sluggish, and usually inconsequential metastatic lesions.

It is our purpose to present the findings in 21 patients in whom bronchial adenoma was diagnosed at the Cleveland Clinic during a period of more than

nine years. Emphasis is placed on the benign course of the disease in these patients so far. The so-called "peripheral" and "multiple" bronchial adenomas reported by Felton, Liebow, and Lindskog,[17] which are thought to originate from the lining epithelium of the bronchioles, are not included in this study.

Material and Methods

The clinical records and pathologic findings in 21* cases of bronchial adenoma were reviewed. All cases were diagnosed at the Cleveland Clinic between January 1948 and May 1957.

Most of the surgical specimens had been removed by either lobectomy or pneumonectomy; consequently the entire neoplasm and any extension was available for study. Multiple blocks, including both endobronchial and extrabronchial portions of the neoplasm were prepared with special consideration given to the margin of the tumor bordering adjacent lung. Special attention was given to all regional lymph nodes that were removed at operation. Histologic specimens were stained routinely by a hematoxylin-eosin—methylene blue stain. Certain sections were stained for the presence of argentaffin granules without success.

Sex and Age

In our series the tumor occurred in 14 women and in 7 men. The ages of the patients ranged from 18 to 73 years, with a mean age of 49 years for the entire group. Six patients were less than 40 years of age.

Symptomatology

The duration of symptoms in 20 patients before the diagnosis was established ranged from 2 months to 20 years, or an average of 5 years. One patient was asymptomatic. The symptoms varied according to the size of the tumor, its location, and the degree of bronchial obstruction that it produced. The three most common symptoms were cough, hemoptysis, and pulmonary suppuration.

A cough was the presenting complaint in 15 of the patients. The cough was slight at onset, but apparently with the growth of the tumor the bronchial irritation increased and the cough became more distressing. Sometimes it was most troublesome at night, or when the patient assumed a particular position (postural cough). In the early stages of the disease, the cough usually was nonproductive. Sputum was present in variable amounts in 11 patients; initially it was mucoid, then, as the growing neoplasm brought about bronchial obstruction and its sequel, pulmonary infection, the sputum became purulent.

**One case was previously reported by one of us (D.B.E.).*[18]

Hemoptysis was one of the common symptoms of bronchial adenoma. It occurred in 11 of the patients and in 2 was the presenting complaint. The hemoptysis was sudden both in onset and in termination; it was not profuse. Usually it was spontaneous in character and independent of any preceding paroxysms or physical effort, and in some of the women it was especially severe during the menstrual period.

Pulmonary suppuration ranging from obstructive pneumonitis through bronchiectasis to frank pulmonary abscess is commonly associated with bronchial adenoma. Bronchiectasis or obstructive pneumonitis or both conditions were present in 15 of the 21 patients.

None of the patients had clubbing of the fingers.

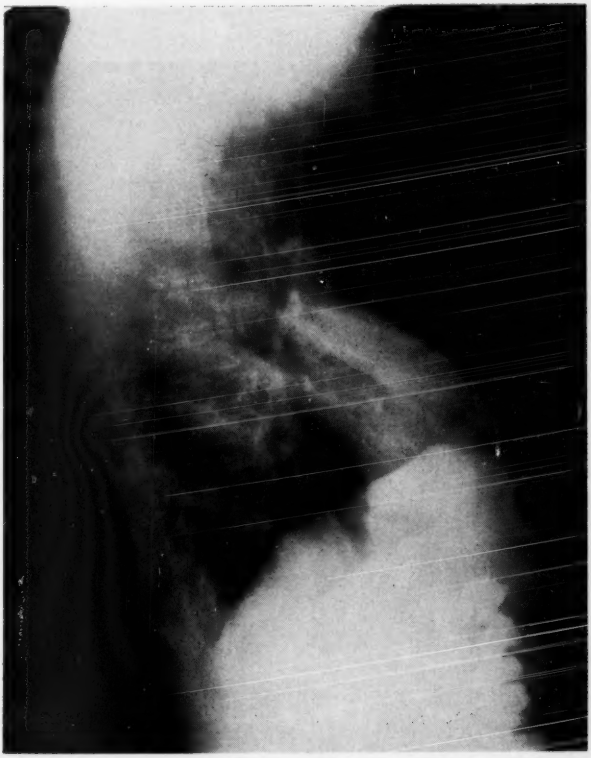

Fig. 1. Total collapse of right middle lobe caused by occlusion of the middle lobe bronchus by bronchial adenoma. The patient was cured by middle lobectomy.

Roentgen Findings

A rather wide range of roentgen findings was visualized. In 10 of the 21 cases the tumor was masked by concomitant inflammatory changes such as distal pneumonitis or thickening of the pleura producing radiopacity of a pulmonary segment or of an entire lobe (Fig. 1). In seven cases the tumor was outlined as a round or an oval opacity without evidence of bronchial obstruction (Fig. 2). In one case roentgenograms showed only a hilar mass. In three cases the roentgen findings of the chest were normal. Bronchiectasis and shifting of the mediastinum were evident in some patients. It must be emphasized that none of these findings were pathognomonic of bronchial adenoma. Whether present singly or in combination, they indicate only a mechanical interference with the normal bronchial drainage. We were unable by roentgen study alone to differentiate an adenoma from other types of bronchial tumors.

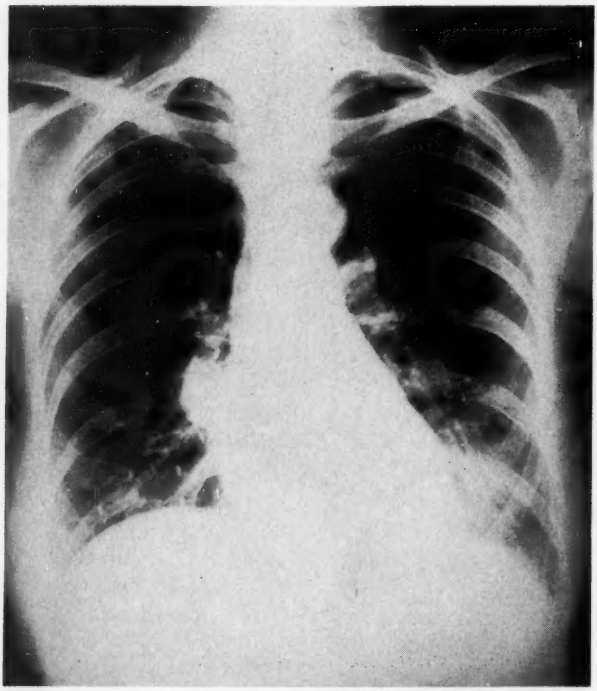

Fig. 2. The circumscribed shadow proved at operation to be caused by bronchial adenoma. It was possible to resect the tumor with its bronchial origin without sacrificing any pulmonary tissue.

Bronchoscopic Findings

Nineteen of the 21 patients underwent bronchoscopic examination. The findings were positive in 15 of the 19 patients, an incidence that is in sharp contrast to that in carcinoma of the lung. In 12 of the 19, the bronchoscopic biopsies were positive for bronchial adenoma. In one, a mass was seen, but a biopsy provided only granulation tissue. The biopsy was not repeated because of severe bleeding at the time of the original examination. In two other instances, tumor was seen, but biopsy was not performed—in one because of the cherry-red, vascular appearance of the external surface, and in the other because the biopsy forceps could not be engaged. Bronchoscopic findings were without significance in four patients.

In two patients, bronchoscopic smears for cytologic study were positive for neoplastic cells (Fig. 3). The bacteriologic findings were without significance. None of the patients had an associated active tuberculous infection.

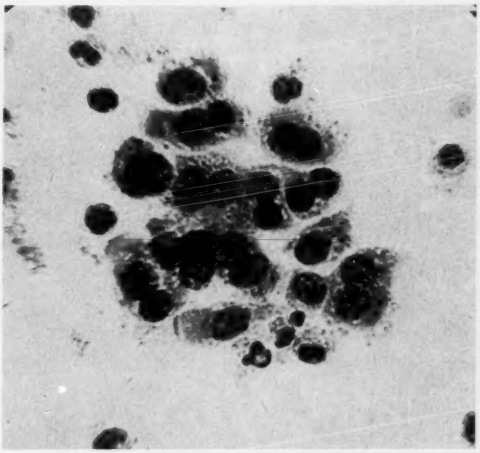

Fig. 3. Neoplastic cells found in bronchoscopic swabbing. Note nuclear stippling. Wet-film preparation stained with toluidine blue; X670.

Pathologic Findings

In our series the tumor occurred with approximately equal frequency in the right and in the left lung. Of those adenomas in the right lung, two involved the right main bronchus, four involved the right upper lobe, two involved the

right middle lobe, and two involved the right lower lobe. Of those adenomas in the left lung, two involved the main bronchus, four involved the upper lobe bronchus, and five originated in the lower lobe bronchus.

In most instances the neoplasm was composed of an endobronchial portion that ranged from 0.5 to 4.0 cm. in diameter, and a much larger extrabronchial portion as great as 7 cm. in diameter (Fig. 4). None of the tumors was entirely

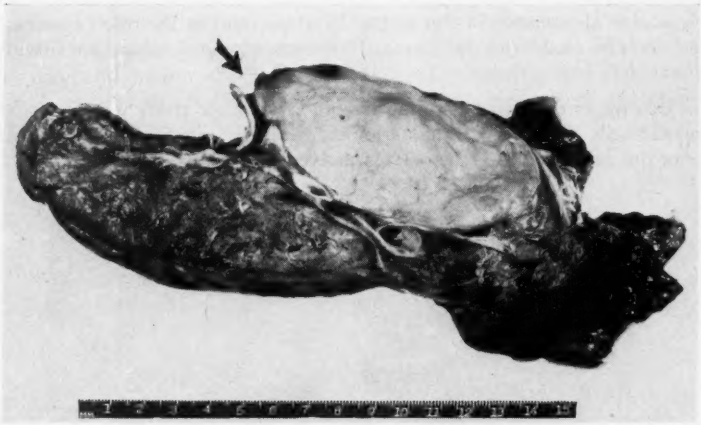

Fig. 4. Large bronchial adenoma; this is a total left pneumonectomy. Note lack of necrosis within the tumor. The arrow indicates the left main bronchus.

endobronchial or intramural. The shape and amount of the endobronchial portion of the neoplasm were no indication of the amount of extrabronchial extension that had occurred. The endobronchial portion corresponded grossly to the bronchoscopist's general description: a polypoid mass, pink to purple, soft to firm, and usually bosselated. The extrabronchial portion usually was sharply demarcated from the adjacent lung. The color ranged from tan to pink to pale gray. Gross necrosis was not noted. In one patient two separate tumors were present involving main bronchi to both upper and lower lobes.

Microscopic sections of the polypoid portion of the adenoma showed an epithelial covering that usually had undergone squamous metaplasia. Areas of ulceration with attached blood clot were occasionally demonstrated. Generally there was a band of fibrous tissue of variable thickness beneath the epithelial layer. The histologic features of the various neoplasms were remarkably constant. The individual cell was of moderate size, with a uniform, round nucleus that commonly showed conspicuous chromatin stippling. The nuclear membrane was distinct. The cellular borders often were indistinct and appeared to

b

a

Fig. 5. The major variations in the histologic features of an adenoma. (a) Typical carcinoid appearance. Hematoxylin-eosin–methylene blue stain; X220. (b) Trabecular arrangement of somewhat larger cells. Hematoxylin-eosin–methylene blue stain; X220.

blend with one another. In the present material, cytoplasmic coloration ranged from pink to gray. Mitosis was uncommon. The cells were arranged into two general patterns within the neoplasm (Fig. 5). Nests and small sheets of these cells closely packed and separated by fine collagenous bands were a prominent feature, with a clustering that most resembled the intestinal carcinoid (Fig 5a). Lumens occasionally were present in the otherwise solid masses. In other regions of the neoplasm, anastomosing cords separated by blood vessels and fibrous strands were prominent (Fig. 5b). Deeply the neoplasm had an abrupt gross junction with surrounding pulmonary tissue. Microscopically, there usually was some evidence of invasion of the lung by small islands of tumor. The blood vessels were profuse among the cords and islands of neoplasm. Although blood vessels occasionally were compressed, there was no evidence of intravascular extension in any of the specimens. In many patients the bronchial cartilages were retained within the tumor (Fig. 6). Only two of the neoplasms showed evidence of osseous metaplasia. In only one tumor was extension to a lymph node demonstrated; the extension was by direct invasion.

Fig. 6. Total mount of a small adenoma. Note the retention of bronchial cartilages within the tumor. Hematoxylin-eosin—methylene blue stain; X5.

Tumor size precluded any attempts to demonstrate origin from mucous glands, although neoplastic islands could be seen intermingled with mucous glands along the bronchial margins of the tumor.

Results of Treatment

In this group all tumors were operable and all 21 patients have remained well. Eleven of the patients were treated by lobectomy and eight by pneumonectomy, one by local resection of the neoplasm through the bronchoscope, and one by removal of the tumor by means of a bronchotomy. The neoplasm removed through the bronchoscope was in the immediate vicinity of the carina. The tumor removed by bronchotomy arose from the left upper lobe bronchus and at the time of operation there was no evidence of extrabronchial growth. The bronchotomy was performed because there was no roentgen evidence of atelectasis. Eighteen months postoperatively the patient was readmitted because of recurrent hemoptysis. A small pea-sized mass was found at the site of the previous operation and a biopsy specimen proved it to be a recurrence of the neoplasm. The roentgen findings, at that time, again did not disclose any evidence of pulmonary change. The patient, who was pregnant, underwent a second bronchotomy for removal of the tumor, and the base of the tumor was cauterized. The patient is being examined at six-month intervals, and there has been no recurrence of the tumor to this date.

Discussion

On the basis of microscopic findings, several classifications and many names have been proposed for bronchial adenomas. The confusion has been such that Liebow[16] was able to collect 27 terms that referred to bronchial adenomas. However, there appears to be increasing agreement that only two major histologic patterns exist, namely, the *cylindromatous* and the *carcinoid*. At the present time many writers recognize the "carcinoid" adenoma and the "cylindroma" as separate entities on the basis of cellular pattern as well as of clinical behavior. The carcinoid adenoma is the commonest of these two types; all 21 of our cases and approximately 90 per cent of all bronchial adenomas reported are of the carcinoid type. We have not seen any examples of the cylindromatous neoplasm in more than 500 primary pulmonary neoplasms diagnosed at the Cleveland Clinic. From the published descriptions of cylindromas they seem to be more invasive than carcinoid adenomas and they often are inoperable. Even when cylindromatous adenocarcinomas of the trachea and bronchi have been treated surgically, they may recur locally and eventually metastasize distantly. According to Clark, Clagett, and McDonald,[19] of all malignant tumors of the trachea, cylindromas are most amenable to treatment because of their slow growth. Although they grow at a slower rate and metastasize less

frequently than bronchogenic carcinomas, in a high percentage of cases they eventually are fatal.

Cylindromas occur most commonly in the trachea but they also occur in the major bronchi. Grossly they are similar to carcinoid adenomas and may grow in the same manner. According to Tinney, Moersch, and McDonald,[20] cylindromas are the second most common malignant tumors of the trachea. In the 15 cases reported by Clark, Clagett, and McDonald,[19] the most frequent symptom was dyspnea caused by a valvular type of obstruction. However, cough, wheezing, hemoptysis, and hoarseness were common symptoms. In six of their patients the tumor was located in the upper third of the trachea; in another six in the lower third; and in the remaining three it was in the middle third of the trachea. The duration of symptoms ranged from four weeks to eight years. The final diagnosis was based upon biopsy findings.

It appears that a difficult situation exists so far as nomenclature of these neoplasms is concerned. The problem of the term "cylindroma" always has been a knotty one. The reason for the diversity of opinion seems, in part, to be a lack of knowledge of the biologic behavior of this neoplasm. Although it appears to metastasize slowly, in most locations in the body, when followed adequately it has been shown to be a relentlessly progressive neoplasm. Undoubtedly, 10 years should be the minimum follow-up interval for this particular group of neoplasms.[21] In salivary gland and nasopharyngeal cylindromatous adenocarcinomas, metastasis may occur long after the patient has been discharged as cured. One such of our tumors of the submaxillary gland did not metastasize until 11 years after the initial surgical operation. The patient still is living several years after the demonstration of pulmonary metastasis. We prefer the term "cylindromatous adenocarcinoma" for such lesions, to the more benign-sounding term "cylindroma."

None of the adenomas in our 21 patients metastasized distantly, but one tumor invaded a regional lymph node. Of the metastasizing "adenomas" reported by others, approximately 55 per cent had metastasized to the regional lymph nodes alone and in the remaining 45 per cent metastasis was present in the following organs in decreasing order of frequency: liver, opposite lung, same lung, pleura, esophagus, bone, brain, kidney, adrenals.

According to published reports, bronchial "adenomas" with distant metastasis were atypical and showed nuclear irregularity, significant pleomorphism, and mitotic figures. All of these changes could be interpreted as indications of a definite increase in malignancy of the tumor. On the other hand, the vast majority of the tumors, like those in our series, which had an orderly carcinoid pattern did not metastasize distantly.

As mentioned previously, a most striking finding in bronchial adenomas is their location either in a primary bronchus or close enough to one so that they are easily accessible to the bronchoscopist. However, words of caution should be interjected at this point. The biopsy of these lesions can be a dangerous procedure. Because of the extreme vascularity of the lesions many bronchoscopists merely like to look at them and note their location without performing

a biopsy. Also, biopsy specimens may show sufficient crushing and distortion of the neoplastic cells to result in an erroneous diagnosis of small-cell carcinoma of the bronchus. The cells, when partially crushed, become dense and spindly. Experience with this distortion, together with a lack of evidence of mitosis, is required to prevent the pathologist from making this diagnostic error.

Although we do not adhere to the concept of an "adenoma syndrome," because of a lack of pathognomonic symptoms of bronchial adenoma, we do believe that the diagnosis of bronchial adenoma should be considered as a possibility in every young adult patient who presents a history of chronic cough with hemoptysis and repeated bouts of pulmonary infections. This is particularly true in female patients, who are statistically less likely to have bronchogenic carcinoma. The prime requisite to the diagnosis of bronchial adenoma is awareness that the lesion may exist and that bronchoscopic studies usually will confirm or refute a suspected diagnosis.

Normal findings on roentgen study of the chest do not exclude the possibility of the existence of an adenoma. Indeed a small-sized neoplasm in a large bronchus, which does not cast a distinct shadow or cause interference with bronchial drainage, may escape detection. In 7 of our 21 cases the tumor was visualized as a circumscribed, solitary nodule on the roentgenogram, as in some of the 23 cases presented by Good and Harrington.[22] Although none of their cases had roentgen evidence of calcification, such calcification was found grossly in one. According to Good, Hood, and McDonald,[23] bronchial adenomas comprise about 8 per cent of the solitary mass lesions of the lung.

Although there is almost unanimous agreement concerning the nature and biologic characteristics of bronchial adenomas, until recently there has not been agreement concerning the most satisfactory method of treating the lesions. About 10 years ago, when the hazards of thoracic surgery still were great, surgeons were reluctant to undertake pulmonary resections except for emergency treatment or for proved malignant lesions. The treatment of choice then was endoscopic removal. Although the recognition of these tumors is possible by bronchoscopy, this examination gives but little specific information as to the degree of extrabronchial extension. Inasmuch as the wholly endobronchial polypoid type of adenoma is unusual, the endoscopist seldom offers the patient a definitive cure.

Cognizance of the anatomic extent and biologic course of these tumors has resulted in abandonment of their bronchoscopic extirpation except as a palliative procedure in the elderly or poor-surgical-risk patient, or in the rare patient in whom the location of the adenoma in the bronchus precludes the successful accomplishment of any other procedure. For example, local removal may be the only feasible treatment of adenomas in the vicinity of the carina. A pedunculated tumor that has a narrow attachment to one of the main bronchi might by choice be treated initially bronchoscopically. However, surgical removal of such a tumor, including its base, with plastic reconstruction of the bronchus would minimize risk of recurrence and at the same time avoid major pulmonary resection.

Almost all patients with bronchial adenomas are good surgical risks, and surgical resection is the treatment of choice. With the present-day development of thoracic surgery, virtually no mortality and but little morbidity need be anticipated regardless of the extent of the resection. Adequate surgical treatment entails complete resection of the tumor and of the irreversibly damaged pulmonary tissue, at the same time preserving as much of the normal pulmonary tissue as possible.

Summary

1. The clinical and pathologic findings in 21 cases of bronchial adenoma are presented. The lesion was twice as frequent in women as in men, and in our series the age groups represented are older than those usually reported.

2. The outstanding clinical symptoms included: cough, hemoptysis, and prolonged suppuration.

3. Bronchoscopic examination of patients having unexplained pulmonary suppuration should lead to earlier diagnosis of bronchial adenoma and consequent lessening of the frequency of chronic pulmonary disability.

4. The histologic pattern in all of the cases was that of the carcinoid variant. None of the neoplasms in this series metastasized.

5. The majority of the patients were treated either by lobectomy or by pneumonectomy and all are now well.

6. Cylindromatous carcinomas of the trachea and bronchi should not be classified as bronchial adenomas.

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USEFULNESS OF ROUTINE SEROLOGIC TESTS FOR SYPHILIS

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ROUTINE serologic tests for the detection of syphilis recently have received criticism relative to their usefulness and cost. The most severe criticism has been leveled against the obligatory premarital blood test that is said to detect relatively few cases of previously undiagnosed syphilis and at a comparatively high cost per test.[1] This concept of the worth of these routine serologic procedures is a reversal of the earlier opinion that the procedures are essential to our national welfare. The earlier opinion resulted in the passage of laws in 40 of the 48 states invoking compulsory premarital examination, and also has affected the standards established by accreditation boards for hospitals.[2] On the other hand, routine serologic tests for syphilis continue to have staunch supporters, especially among public health workers.[3-5] Collen and Linden[6] reported favorably on the usefulness of serologic screening in prepaid group-practice plans.

Magnuson, Donohue, Stuart, and Gleeson[7] of the Public Health Service recently discussed the advantages of premarital serologic tests for syphilis, which in most states are part of a physical examination. Among the advantages listed are: detection of syphilis; prevention of transmission of syphilis between marital partners; provision of the physician with an opportunity to give health education, sex education, and marriage counseling; detection of other diseases; and provision of an index of the prevalence of syphilis. These authors stated that reactivity rates in premarital blood testing had not declined in the years 1951-1954, the only period for which data were available, and that conservative estimates indicated that 12,000 to 13,000 persons having previously untreated syphilis were found annually through premarital blood testing. They expressed the belief that if through the premarital blood testing only a small percentage of these persons were protected from infecting their subsequent spouses and thereby avoiding congenital syphilis in their offspring, routine testing would result in the prevention of a considerable number of new cases of syphilis.

Since the opening of the Cleveland Clinic in 1921, serologic tests for syphilis have been performed as one phase of our routine laboratory survey, which consists of determination of hemoglobin concentration, cell volume, white blood cell count, blood sugar value, and urinalysis. This work is part of the routine examination of all new patients and any former patients for whom complete re-examination is requested.

Because it has been our belief that the routine serologic tests are useful, it was decided to review our records to determine more accurately the status of

these tests. Since we routinely perform both the Kolmer complement-fixation test and the Kahn test, the records also were analyzed to ascertain the relative merits of the two tests.

Material and Method

Data were analyzed on the basis of three groups of findings: group I comprised findings in 340 patients in whom serologic tests for syphilis were positive; group II comprised findings on 501 premarital serologic tests; group III comprised findings on serologic tests of approximately 3,000 professional blood donors.

All of the specimens included in the study were examined by using both the Kolmer complement-fixation test and the Kahn test. The antigen used in the two-tube complement-fixation test was Kolmer's cardiolipin antigen prepared by the Sylvana Chemical Company. The three-tube Kahn test followed the usual accepted Kahn technic, using the Standard Kahn Antigen prepared in Doctor Kahn's laboratory at the University of Michigan. All tests in which the results were positive or doubtful were repeated and then the specimens were submitted both to the Kolmer and to the Kahn quantitative procedures.[8] When it was requested by the attending physician, sera were referred to the serology laboratory of Mount Sinai Hospital, in Cleveland, for the Kline test, or to the University of Michigan for the *Treponema pallidum* immobilization (TPI) test.

Group I. This group includes those patients in whom serologic tests for syphilis were positive. Review of 12,396 blood specimens that were submitted to our laboratory for serologic tests for syphilis during a four-month period (June 1 through September 30, 1955) showed that 516 specimens from 340 patients were reported as positive.

Of the 12,396 specimens, 9,851 were from new patients who were undergoing routine laboratory surveys. Most of the others were from former patients who were being restudied; however, a small number of these specimens were submitted for premarital blood tests, for pre-employment surveys, or for rechecking a previously reported positive test.

A complete review was made of 313 charts, and it was possible to subdivide the group of patients as follows: 114 newly admitted patients having syphilis; 64 patients in whom syphilis had been previously diagnosed here; 60 patients having biologic false-positive tests for syphilis; and 75 patients for whom complete follow-up data were not available. The differentiation for the first two subgroups was an arbitrary one. Among those classified as newly admitted patients having syphilis were included all patients in whom the diagnosis of syphilis had not previously been made here, even when the diagnosis had been made elsewhere prior to the patient's being seen here.

The greater sensitivity of the complement-fixation test as compared with the Kahn test is obvious from the results in the 114 newly admitted patients. Sixty-

one, slightly more than half (Table 1), of the 114 diagnoses were based on the serologic findings and would not have been made if the routine serologic tests had not been performed. The results of the Kolmer test were positive in all but 2 of the 114, and in approximately one third of these patients there was a negative Kahn in the presence of a positive Kolmer test. Twenty-five of the 61 patients in the first two categories listed in Table 1 began treatment here, while most of the remainder were treated elsewhere. Of the entire group there was only one patient with primary syphilis who, at the time of admission, had positive findings on dark-field examination.

Table 1.—*Basis of diagnosis in newly admitted patients having syphilis, during a four-month period*

Basis of diagnosis	Results of serologic tests, no. of patients			Total no. of patients
	Kolmer *positive* Kahn *negative*	Kolmer *negative* Kahn *positive*	Kolmer *positive* Kahn *positive*	
Serologic test alone, no history of disease admitted	6*	2	21**	29
Serologic test, history of infection obtained subsequently	8	0	24**	32
History of infection given on admission, confirmed by serologic test	14	0	22	36
Clinical symptoms suggesting syphilis, confirmed by serologic test	8	0	9	17
Total	36	2	76	114

**TPI test performed on 2 specimens, result positive in each.*

***TPI test performed on 1 specimen, result positive.*

Many of the 64 patients having previously diagnosed syphilis had been coming to the Cleveland Clinic for years, and the initial diagnosis of syphilis had been made and treatment had been instituted here. An analysis of these data in treated syphilis (Table 2) continues to demonstrate the greater degree of sensitivity of the Kolmer test as compared with the Kahn test.

Table 2.—*Results of serologic tests in patients having previously diagnosed syphilis, during a four-month period*

Results of serologic tests	Number of patients		
	Symptomatic for syphilis at time of serologic tests	Asymptomatic for syphilis at time of serologic tests	Total
Kolmer *positive*) Kahn *positive*)	7	28	35
Kolmer *positive*) Kahn *negative*)	6	18	24
Kolmer *negative*) Kahn *positive*)	3	2	5
Total	16	48	64

Sixty patients were classified as having biologic false-positive tests because there was no evidence to suggest syphilitic infection except positive results of either the Kolmer or the Kahn test or both, or there was a clinical diagnosis in which a false-positive serologic test for syphilis was a common finding. Each attending physician had his own method of arriving at the decision to accept the result of our determination as being false-positive (Table 3). The clinical features that seemed to exclude syphilis are represented in a variety of cases. For example there was an 80-year-old moribund woman who previously had had numerous negative serologic tests here; and there was a five-year-old boy who before had had many negative serologic tests for syphilis and whose parents had negative serologic tests and no history that might indicate association with the disease. Repeated serologic tests were negative in 19 (almost one third) of the 60 patients. This percentage of repeated negative serologic tests compares favorably with the experience of other workers.[6]

In those patients regarded as having false-positive tests the high degree of sensitivity of the Kolmer test with its associated lack of specificity is shown to be a disadvantage, since nearly half of the false-positive tests reported were on the basis of positive Kolmer and negative Kahn tests.

The final subgroup consists of the 75 patients for whom complete follow-up reports were not available. Twenty-five of the 75 patients were treated here for another disease and were referred back to their own physicians for follow-up of their positive serologic findings. Another 15 of the 75 were too ill from other diseases to be concerned about positive serologic tests; most of these patients had malignant neoplasms and died during the course of the study. Three patients of the subgroup failed to return to the Clinic for further study.

Group II. During the six-year period of the survey (March 10, 1951, to March 10, 1957), 501 persons had the special premarital serologic tests which are

Table 3.—*Basis for classification of false-positive serologic tests during four-month period; all patients asymptomatic for syphilis*

Basis for classification	Results of serologic tests, no. of patients: Kolmer *positive* Kahn *negative*	Kolmer *negative* Kahn *positive*	Kolmer *positive* Kahn *positive*	Total no. of patients
Clinical situation excluded syphilis	9	2	12	23
Clinical situation excluded syphilis, but recheck serologic test recommended	2	0	1	3
Repeated serologic test *negative*	14	3	2	19
Kline test *negative*	0	0	2	2
Cerebrospinal fluid test *negative*	1	0	4	5
Cerebrospinal fluid test and TPI test *negative*	1	1	2	4
TPI test *negative*	1	1	2	4
Total	28	7	25	60

performed in conformity with the law of the State of Ohio. No new cases of syphilis were found. Seven patients whose serologic test results were reported as positive were under treatment at the time or had completed their treatment here or elsewhere.

A review of this roster of premarital applicants indicates that it was not a cross section of the general population but was heavily weighted by a large number of professional people and their families, who as a population group have an extremely low incidence of syphilis. Twenty-five (5 per cent) of the 501 persons listed on the roster were physicians.

Group III. During the past seven years (1950 to 1957), we have drawn 11,958 units of blood from approximately 3,000 professional donors. Of this group only three potential donors have been rejected because of positive serologic determinations for syphilis. In each case an interview indicated that the person although unaware of his infection was not surprised by the positive results. In all three patients treatment was instituted promptly. Group III is similar to the premarital group in that it also is not representative of the general population, as many of the donors are students in colleges or professional schools, or are

members of our staff or are our employees, groups that would be expected to have a low incidence of syphilis.

Discussion and Summary

Routine serologic tests for syphilis appear to be useful. Not only are many cases of previously undiagnosed syphilis found, but attention is focused on many previously diagnosed cases, some of which require more adequate treatment. Some patients are inaccurate in answering questions about a possible history of venereal disease, and sometimes even in the presence of unmistakable clinical evidence they will admit to having a history of syphilis only after a positive serologic test has been reported to them. The importance of accurate diagnosis is obvious. While many of the newly admitted patients having syphilis had had previous medical care, it is important that the diagnosis be recognized at the time of the routine test, for the sake of sound medical practice. However, a goodly number of these patients (32 of 114) classified as newly admitted patients having syphilis did receive treatment at the Cleveland Clinic either during the time covered by this survey or subsequently.

The performance of the sensitive Kolmer complement-fixation test appears to be excellent. In a test of this type, sensitivity is obtained at the expense of specificity; nearly half (28 of 60) of the false-positive serologic tests were based on positive Kolmer tests and negative Kahn tests. However, 60 of the 177 diagnoses of syphilis would have been missed on the initial survey if only the Kahn test had been used. The usefulness of the Kahn test is related to its specificity; only seven of the patients having false-positive tests had been reported to have a positive Kahn test and a negative Kolmer test.

The usefulness of the premarital blood test seems to be slight in our clinic practice. Although the series is too small to be really significant, nevertheless the results indicate that premarital serologic tests for syphilis have little application in the population served by us.

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